Detection of perimacular red dots and blots when screening for diabetic retinopathy: Refer or not refer?

Brief Report

DETECTION OF PERIMACULAR RED DOTS AND BLOTS WHEN SCREENING FOR DIABETIC RETINOPATHY. REFER OR NOT REFER?

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Abstract

Purpose: Detection of microaneurysms and/or microhaemorrhages near the fovea when screening for diabetic retinopathy (DR) poses a problem because referral to retinal specialists may alarm patients and unnecessarily burden ophthalmologists.

Methods: Six-month prospective study of patients found to have minimal red lesions within one disc diameter of the fovea when screened for DR. Two 45° digital photographs, one centred on the macula and the other nasal including the optic disc, were taken for each eye. All patients received a 6-month re-screening appointment.

Results: Out of 70 patients, 41 returned for re-screening. DR had worsened in 3, who required referral but no treatment, was unchanged in 19 and undetectable in the other 19. HbA1c decreased from 7.76±1.50% (61.3±16.2 mmol/mol) to 6.93±1.7 (52.3±18.9 mmol/mol) in the patients in whom DR worsened but did not change in the other groups. Baseline HbA1c ($p=0.048$) and systolic blood pressure ($p=0.007$) were lower in the patients in whom DR improved, but a multivariate model including HbA1c, blood pressure and known disease duration could not identify any independent risk factor.

Conclusion: Minimal red lesions near the fovea, though commanding early re-screening, do not require immediate referral to retinal specialists.

Key words: Diabetic retinopathy, screening, diabetic macular edema, microaneurysms.

Introduction

Screening for sight-threatening retinopathy ranks among the most cost-effective procedures in health care (1,2). Protocols and guidelines are well in place (3-5) but evidence for some aspects of the screening process remains to be strengthened. In particular, little is published on how to proceed when isolated red lesions, i.e. microaneurysms and/or microhaemorrhages, are identified by retinal photography near the fovea (6,7). On the one side, since the macula is the centre of vision, minimal lesions should not be overlooked by graders, especially if they are not retinal specialists, when screening is carried out on bi-dimensional colour photographs which do not permit detection of retinal thickening and macular edema. On the other hand, referral of minimal lesions may place unnecessary burden on retinal specialists and alarm on patients.

Based on these premises, a prospective observational study was carried out in patients who, when screened in our Diabetic Retinopathy Centre, were found to have red lesions within one optic disc diameter of the centre of the fovea, in the absence of other signs of more severe DR.

Methods

Screening for diabetic retinopathy (DR) in our Centre includes collection of clinical data, measurement of visual acuity by decimal charts and intraocular pressure by insufflation tonometry, and induction of mydriasis by 1% tropicamide eye drops. Two 45° digital photographs of the retina are taken by a Kowa Pro-II funduscamera, one centred on the macula and the other nasal to, though including, the optic disc. All images were visualized by the EyeCap software (Haag-Streit, Koeniz, Switzerland), evaluated by a medically qualified grader (AB) and included in this study if they showed any red dots and blots within one disc diameter of the centre of the fovea. Exclusion criteria were: previous evidence of DR involving the macular area, presence of hard exudates or any other lesions requiring referral according to Italian guidelines (5), previous retinal treatment by photocoagulation and/or intraocular agents, presence of other systemic conditions, e.g. renal failure or cancer, potentially impacting on retinal status and/or shortening life expectancy.

According to current Italian guidelines (5), patients with mild non proliferative DR at the posterior pole were given a 6-month appointment for re-screening, which included the procedure described above and grading by the same observer. The lesions were classified as improved if no longer visible, stable if still detectable on the images, and worse if larger/more numerous than at baseline. Worsening of DR involved referral to an ophthalmologist whereas persistence/improvement of the lesions observed at baseline indicated another 6-month screening appointment. Enrolment was from

January 2015 through to March 2017. All photographs were reviewed by a second independent grader (MP) and, in the case of discordance, discussed and adjudicated by the two graders together. Diabetes was classified as type 1 if onset had been before age 30 and insulin started within 1 year of diagnosis, and type 2 if onset had been after age 40 and insulin treatment was either not in place or started more than 1 year after diagnosis.
Ethical clearance for the study and informed consent were obtained from the patients, according to the tenets of the Helsinki Declaration.

Statistical analysis. Descriptive data are shown as absolute and relative frequencies of the different modalities for categorical data and as mean ± standard deviation (SD) for continuous variables. At univariate analysis, t-test for continuous variables and chi-square test for qualitative variables were carried out to detect the possible predictors of DR progression by comparing clinical characteristics at baseline between the improved and stable/worsened group. Multivariable analysis models were then fitted to evaluate the independent effect of the variables that turned out to be significantly associated to DR status at univariate analysis: DR group at 6 months (stable/worsened versus improved group) was set as the dependent variable of a logistic regression model where known diabetes duration, systolic blood pressure and HbA1c at baseline were taken as independent variables. For all tests, a p value of less than 0.05 was considered significant. All analyses were performed with Stata 14.

Results

In total, 70 patients were enrolled, 42 men and 28 women, 17 with type 1 diabetes, 52 with type 2 and 1 with secondary post-pancreatectomy diabetes. Mean age was 56.7 ± 15.7 and known disease duration 15.0 ± 10.6 years. Of these, 41 returned for the 6-month re-screening visit. DR had worsened in 3 of them and required referral, was unchanged in 19, and undetectable in the remaining 19.
All 3 patients in whom DR worsened had type 2 diabetes. Two were females, age was 60.3 ± 2.5, known diabetes duration 8.7 ± 5.5 years, and systolic blood pressure 142.3 ± 15.3. Their serum creatinine was 0.81 ± 0.38 mg/dl (eGFR 107.3 ± 30.2 ml/min), serum cholesterol 161.3 ± 28.2 mg/dl, HDL cholesterol 51.7 ± 12.1 mg/dl, and trigyceride 135.0 ± 27.0 mg/dl. Interestingly, the mean HbA1c of these 3 patients had decreased from 7.76 ± 1.50% (61.3 ± 16.2 mmol/mol) at baseline to 6.93 ± 1.7 after 6 months (52.3 ± 18.9 mmol/mol) while it did not change in the other two groups. Of these 3 patients, 2 were on oral agents and 1 on insulin, 2 on inhibitors of the renin-angiotensin system and none on statins.

Because of the low numbers, for statistical purposes, the 3 patients in whom DR had worsened were grouped with the 19 in whom DR had remained stable and compared for risk determinants with those in whom the lesions had cleared. The clinical characteristics of these two groups are shown in Table 1.

Univariate analysis showed that baseline HbA1c ($p=0.048$) and systolic blood pressure ($p=0.007$) were lower in the patients in whom DR had improved over the following 6 months. However, a multivariate analysis model including these two variables and known disease duration could not identify any independent risk factor (Table 2).

Eighteen patients returned for screening after 12 months of baseline, of whom 1 had not attended at 6 months, but in none of them had DR worsened.

Discussion

This study shows that minimal lesions (red dots and blots) detected by digital retinal photography in the macular area at the time of screening for DR do not warrant immediate referral to an ophthalmologist. Of the patients with these characteristics, only 3 deteriorated marginally to require specialist attention but did not proceed to photocoagulation or other forms of treatment for DR, whereas the lesions either stabilised or even disappeared over 6 months in the other patients. These findings are in line with the results of two other studies that investigated similar groups of patients although considering only ophthalmological outcomes. One of them was also prospective and reported no development of clinically significant macular edema over 9-months of follow-up (6). The other was a cross-sectional study in which patients with minimal peri-foveal lesions were evaluated by optical coherence tomography (OCT), reporting that suspicion of macular involvement on the basis of retinal photography alone carries a false-positive rate of 86.6% (7). In this paper, we also collected a series of clinical data to search for possible systemic risk factors associated with the outcome of such retinal lesions.

This study has limitations. The number of patients enrolled is low but, as this clinic has a turnover of about 3,000 screening episodes per year, the fact that it took more than 2 years to collect the sample is testimony to the relative rarity of the condition investigated. This limited the possibilities of identifying clinical risk factors that would help to single out patients at risk of progression of DR. As expected, those who regressed had lower systolic blood pressure and HbA1c, in line with the literature (8), but neither remained as an independent risk factor when multivariate analysis was carried out. Nevertheless, special care should be applied to bring these variables to target, if elevated. On the other hand, the 3 patients whose DR worsened did not have poor control of blood pressure or high HbA1c to start with. Indeed, their HbA1c decreased to a larger extent than in the

other patients. The relatively modest rate of HbA1c decrease suggests but does not fully support a phenomenon of “early worsening” of DR, which was described for larger rapid improvements of metabolic control in type 1 (9) and type 2 diabetes (10). Measurements of retinal thickness by Optical Coherence Tomography (OCT) should have complemented the study of these patients (7), but the instrument was not available to us for screening purposes. Assessment of DR was on bi-dimensional digital photographs by two expert medically qualified graders and there was no significant drop in visual acuity. Finally, the dropout rate of 29 patients who, out of 70, failed to return for their 6-month appointment, despite being warned that a potentially serious condition was detected in their eyes, is worrying and points to the need for efficient recall mechanisms to be put in place.

In conclusion, this study confirms that presence of minimal red lesions near the fovea, though commanding early re-screening, does not require immediate referral to retinal specialists. Potentially, the addition of OCT to the screening procedure, may help identify patients in need of stricter follow up.

Authors’ contributions

M.P conceived the study, researched the data and wrote the manuscript. A.B., E.S., M.T., A.M., acquired the data and revised the manuscript. F.C. and L.C. interpreted the data and revised the manuscript. All authors approved this version of the manuscript.

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Authors’ conflict of interest: none to declare.

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Table 1. Comparison of the patients in whom DR improved and in whom DR remained stable or worsened.

	Improved (n=19) Baseline		**Stable/Worsened (n=22) Baseline**		**p value***
Type 1 diabetes Type 2 diabetes	4 15		4 18		0.817
Males	10 (52.6%)		14 (63.6%)		0.476
Active smokers	11 (57.9%)		12 (54.6%)		0.427
Age (years)	58.2 ± 15.6		59.2 ± 11.9		0.814
Known duration of diabetes (years)	14.3 ± 10.1		16.3 ± 10.2		0.532
Treatment: Diet only Oral agents Insulin Oral agents + insulin	0 (0%) 11 (57.9%) 4 (21.1%) 4 (21.1%)		1 (4.5%) 12 (54.6%) 5 (22.7%) 4 (18.2%)		0.816
	Baseline	**6 months**	**Baseline**	**6 months**	
BMI	28.5 ± 4.9	28.1 ± 5.0	28.3 ± 4.5	28.4 ± 4.6	0.875
HbA1c(%)	**7.1 ± 0.9**	7.0 ± 1.1	**8.6 ± 2.7**	8.1 ± 2.7	**0.048**
HbA1c (mmol/mol)	**54.3 ± 9.7**	52.9 ± 12.4	**69.9 ± 28.9**	64.6 ± 28.6	**0.048**
Systolic blood pressure (mmHg)	**130.2 ± 13.7**	129.8 ± 14.9	**145.4 ± 18.4**	141.9 ± 20.1	**0.007**
Diastolic blood pressure (mmHg)	77.4 ± 12.0	77.4 ± 12.5	79.6 ± 9.7	81.4 ± 13.4	0.534
Serum creatinine (mg/dl/)	0.91 ± 0.3	0.89 ± 0.33	0.79 ± 0.2	0.81 ± 0.2	0.174
eGFR (ml/min)	94.1 ± 35.51	95.1 ± 36.8	101.3 ± 26.2	101.78 ± 34.8	0.492
Total cholesterol (mg/dl/)	168 ± 30.59	162.6 ± 29.8	173.2 ± 40.9	170.4 ± 47.3	0.680
HDL cholesterol (mg/dl/)	55.7 ± 18.3	53.3 ± 17.8	57.2 ± 17.4	57.1 ± 14.3	0.811
Triglyceride (mg/dl/)	107.1 ± 39.9	110.4 ± 45.2	123.6 ± 58.4	104.8 ± 42.4	0.345
On ACEi/ARB	6 (31.6%)	6 (31.6%)	9 (42.9%)	10 (45.5%)	0.635
On statins	5 (27.8%)	5 (27.8%)	6 (27.3%)	6 (27.3%)	0.955
DR – Right eye Left eye Both eyes Absent	9 (47.4%) 10 (52.6%) 0 0	0 0 0 19 (100%)	12 (54.5%) 6 (27.3%) 4 (18.2%) 0	11 (50%) 8 (36.4%) 3 (13.6%) 0	0.113

*p-values refer to comparisons between the patient groups at baseline

Table 2. Multivariate analysis for DR progression predictors.

Clinical characteristics at baseline	Odds Ratio	95% CI	p value
Known diabetes duration	.98	.89-1.07	0.702
Systolic blood pressure	1.04	.99-1.10	0.068
HbA1c	2.16	.78-5.99	0.139